REMARKS/ARGUMENTS

Claims 21 and 22 are canceled as redundant without prejudice. Claims 1, 6, 14 and 20 are amended. Claim 25 is added. The support for this claim may be found on page 6, under the subtitle "Compositions." Claims 1-20 and 23-25 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

The Examiner maintained the rejection of claims 14-17, 19, and 20 under 35 U.S.C. 102(e) over publication US 2002/0081302 of the U.S. Patent Application by Cvitkovitch et al. (Cvitkovitch). This rejection is respectfully traversed.

The Examiner refers to §085 of Cvitkovitch as disclosing "a vaccine where the CSP provides protection against carries" and §84 as disclosing "CSP in toothpaste, mouthwashes or chewing gum."[1] The Examiner then concludes that "[i]nherently the toothpaste, mouthwashes or chewing gum (medicament) would have the capability of preventing attachment of *S. mutans* to teeth." Applicants disagree with this reading of Cvitkovitch.

To constitute an anticipatory reference, the prior art must contain an enabling disclosure *Chester v. Miller*, 906 F. 2d 1574, 1546 n. 2 (Fed. Cir. 1990); see also *Titanium Metals Corp. v Banner*, 778 F. 2d 775, 781 (Fed. Cir. 1985). A reference contains an enabling disclosure if a person of ordinary skill could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself, and thereby the public, in possession of the invention. *In re Donohue*, 766 F. 2d 531, 533 (Fed. Cir. 1985).

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[1] Since §84 consists of one word "Vaccines," applicants presume that it was the Examiner's intention to refer to §79 instead of §84 for the teaching of toothpaste, mouthwashes or chewing gum.

Cvitkovitch fails to provide an enabling disclosure of a medicament for the treatment or prophylaxis of a condition associated with the attachment of *S. mutans* to teeth, comprising an isolated CSP in an amount effective to reduce the attachment of *S. mutans* to teeth. As discussed in the applicants' amendment filed on February 22, 2004, Cvitkovitch describes competitive inhibitors of CSP for treatment of caries. Cvitkovich does not provide an enabling disclosure of using CSP itself. The position of applicants is supported by the prosecution history of Cvitkovitch's application.

All claims of Cvitkovitch's application, which were directed to vaccine compositions, were rejected by the Examiner as not enabled. The Examiner explained (Office Action dated December 13, 2002, pp 4—5):

> "Claims are drawn to a pharmaceutical composition or vaccine composition comprising compounds that competitively inhibit binding of CSP (competence signal peptide) to *S. mutans* histidine. ***Compound is a peptide*** or an antibody. Enablement of a "pharmaceutical composition" or "vaccine" is considered to rest on a teaching of *in vivo* administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed pharmaceutical compositions/vaccine is for the treatment of dental caries. Thus, the nature of the invention is a therapeutic composition used in the treatment of dental caries caused by *S. mutans*.
>
> Although the specification discloses the claimed composition, and general methods for formulating compositions in pharmaceutically acceptable carriers, there is ***insufficient guidance which would enable one skilled in the art to use***

the claimed compositions for their intended purpose, viz., for the generation of a protective immune response against dental caries.

At the time the invention was made, vaccines comprising the claimed products, SEQ.ID.NO: 2 or 4 (i.e., in vivo) were not routinely used and is unpredictable since the art recognizes that in vitro activity does not correlate with in vivo efficacy.

(1) The compound/peptide may be inactivated before producing a sufficient effect, e.g. such as proteolytic degradation, immunological inactivation.

(2) The compound may have poor bioavailability (e.g. may be adsorbed or absorbed by fluid), and

(3) A large enough effective local concentration may not be capable of being established even with administration of excess amounts, particularly as such relates to ensuring that adverse side effects do not occur that would prohibit use of such compound in therapy. See M.P.E.P. 608.01(P) and Ex parte Aggarwal, 23 USPQ2d 1334 1337 1338 (BPAI 1992). Benet et al., 1990, in The Pharmacological Basis of Therapeutics, Gilman et al., eds. Pergamon Press, New York, pp. 3-32. ***The specification lacks guidance by way of general methods or working examples, which teach an "effective amount" of peptide, or antibody, which would be used for this purpose.*** Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as immunotherapy of dental caries. ***It is unpredictable whether the claimed pharmaceutical composition,***

> ***which is disclosed as being immunogenic, would have the added property of generating an immune response sufficient to inhibit dental caries***, because the specification has not disclosed a link or nexus between the generation of protective immunity and its use in preventing dental caries. Further, it is not routine in the art of immuno therapy to use compositions analogous to the claimed compositions for this purpose. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition/vaccine for its intended use. Therefore, ***undue experimentation would be required*** to make and use the invention." (emphasis added)

In his response to this Office Action, Cvitkovitch deleted all claims directed to vaccine compositions (amendment filed on April 17, 2003). With respect to the remaining in the application claims, Cvitkovitch stated that "each of those claims is ***not drawn to a pharmaceutical composition or vaccine composition***, but is instead directed to an isolated polypeptide having competence signal peptide activity." (emphasis added)

Because Cvitkovitch does not provide an enabling disclosure of a medicament for the treatment or prophylaxis of a condition associated with the attachment of *S. mutans* to teeth, comprising an isolated CSP in an amount effective to reduce the attachment of *S. mutans* to teeth, he does not anticipate claims 14-17, 19, and 20 or make them obvious. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1-6 and 14-24 are rejected under 35 U.S. 112, first paragraph, "because the specification, while being enabling for a composition comprising an

isolated Competence Stimulating Peptide (CSP) and sucrose, wherein the CSP comprises SEQ ID NO:1, does not reasonably provide enablement for a modification thereof. This rejection is moot with respect to claims 21 and 22 due to the cancellation of the claims. With respect to claims 1-6, 14-20, and 23-24, the rejection is addressed below.

As stated in their previous response, applicants respectfully submit that a person of ordinary skill in the art would know how to use modern bioinformatics methods coupled with protein structure modeling software to identify conservative modifications of SEQ ID. NO:1, including additions and deletions of amino acids, that will not affect CSP structure. After such conservative modifications are identified, only routine experimentation would be required to use the assay of the present invention to determine whether the modified CSP peptide retains its function of reducing attachment of *S. mutans* to teeth. However, in order to expedite the prosecution of the instant application, applicants amended the independent claims 1 and 14 by deleting the phrase "a modification thereof." Applicants will pursue claims that include modifications of CSP in a continuing application. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1-6 and 14-24 are rejected under 35 U.S.C. 102 (e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Cvitkovitch. This rejection is moot with respect to claims 21 and 22 due to the cancellation of the claims. With respect to claims 1-6, 14-20, and 23-24, the rejection is respectfully traversed.

Examiner states that claims 1-6 and 14-24 are drawn to a composition comprising CSP and sucrose, wherein the CSP is capable of preventing the attachment of *S. mutans* to teeth. Examiner then substantially repeats her earlier argument of Cvitkovitch disclosing "a compound that competitively inhibits binding of CSP to *S. mutans* histidine kinase" that can be delivered "by topical application,

alone or in combination with other compounds including toothpaste." The Examiner than concludes that "[i]nherently the claimed compositions would have sucrose in the toothpaste." Applicants disagree.

First, applicants would like to clarify that independent claim 14 and its dependent claims 15 and 18-20 and independent claim 24 do not require sucrose. Second, as discussed in detail above, because Cvitkovitch does not provide an enabling disclosure of a medicament for the treatment or prophylaxis of a condition associated with the attachment of *S. mutans* to teeth, comprising an isolated CSP in an amount effective to reduce the attachment of *S. mutans* to teeth, he does not anticipate claims 1-6, 14-20, and 23-24 or make them obvious.

Additionally, with respect to claims 1-6, 16, 17, and 23 that require a combination of CSP and sucrose, applicants would like to note that teaching of administering a compound with a toothpaste does not inherently teach presence of sucrose. Although inherency is a legally viable method for interpreting a reference, the "examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Inherency, however, may not be established by probabilities or possibilities. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749-50 (Fed.Cir.1991).

Cvitkovitch does not teach desirability of a sugar, much less sucrose, in his toothpastes. Moreover, sugars, in general, and sucrose, in particular, are thought by those skilled in the dental arts to be undesirable in dental hygiene products. To support this point, applicants include several publications and a survey of consumer information on toothpaste sweeteners.

The article by D.T. Zero, entitled "Sugars – The Arch Criminal?", Caries Res. (2004), 38:277-285 (Attachment 1), stresses role of sucrose in causing caries and

suggests replacement of sucrose with monosaccharides to reduce incidents of caries (see pp. 282-283, in particular). The article by P.J. Moynihan, entitled "Update on the nomenclature of carbohydrates and their dental effects," J. Dentistry (1998), Vol. 26, No. 3, pp. 209-218 (Attachment 2), reviews various natural and synthetic carbohydrates in their ability to cause tooth decay. The article notes that sucrose "appears to be the most cariogenic sugar" (p.210, right column) and suggests using non-sugar sweeteners, such as polyols, as a safer alternative for teeth (p. 216).

The Summary of Consumer Information on Toothpaste Sweeteners (Attachment 3), provides applicants' survey of web sites of toothpaste manufacturers and demonstrates that toothpastes are usually sweetened with sodium saccharin. A few exceptions are "natural" toothpastes that contain synthetic sugar alcohols (xylitol, sorbitol), but certainly not sucrose. The FAQ sections on the web sites reflect consumer concern with the safety of saccharin. The manufacturers have to dispel consumer fears by asserting that saccharin is not dangerous and its use is unavoidable.

In summary, current toothpaste and other dental hygiene formulations contain synthetic sweeteners to avoid use of sucrose as the most cariogenic sugar. Accordingly, by mentioning delivery of his compounds with toothpaste, Cvitkovitch does not inherently teach using a combination of his compounds with sucrose. Accordingly, applicants respectfully request withdrawal of the rejection of claims 1-6, 14-20, and 23-24 over Cvitkovitch.

Applicant believes the foregoing amendments comply with requirements of form and thus may be admitted under 37 C.F.R. § 1.116(b). Alternatively, if these amendments are deemed to touch the merits, admission is requested under 37 C.F.R. § 1.116(c). In this connection, these amendments were not earlier presented because they are in response to the matters pointed out for the first time in the Final Office Action.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
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